INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 94/00896

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9209564	11-06-92	AU-A-	9017391	25-06-92
		AU-A-	9023391	25-06-92
		EP-A-	0489577	10-06-92
		EP-A-	0489579	10-06-92
		WO-A-	9209565	11-06-92
		GB-A-	2255339	04-11-92
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		HU-A-	61973	29-03-93
		JP-T-	5503719	17-06-93
		JP-T-	5503720	17-06-93
		US-A-	5300501	05-04-94
EP-A-0489577	10-06-92	AU-A-	9017391	25-06-92
		AU-A-	9023391	25-06-92
		EP-A-	0489579	10-06-92
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		GB-A-	2255339	04-11-92
		GB-A-	2255340	04-11-92
		HU-A-	61973	29-03-93
		JP-T-	5503719	17-06-93
		JP-T-	5503720	17-06-93
		US-A-	5300501	05-04-94
WO-A-9102716	07-03-91	AU-B-	639706	05-08-93
		AU-A-	6045490	03-04-91
		EP-A-	0489032	10-06-92
		JP-T-	5501864	08-04-93

INTERNATIONAL SEARCH REPORT

I. .rnational application No.
PCT/GB94/00896

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 1,10: The term "prodrugs" is not clear and it is not possible to determine which compounds are meant by it. The scope of the search do not include prodrugs, except to the extent to which they may be covered by the broad definition of the remaining part of the Markush formula in claim 1.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PC1/GB 94/00896

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C323/60 A61K31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 09564 (CELLTECH) 11 June 1992 cited in the application see page 2 - page 3	1,11,12
A	EP,A,0 489 577 (CELLTECH) 10 June 1992 see page 2 - page 3	1,11,12
A	WO,A,91 02716 (BRITISH BIO-TECHNOLOGY) 7 March 1991 see page 7 - page 9	1,11,12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 1994	29. 06. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	English, R

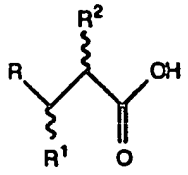
Form PCT/ISA/210 (second sheet) (July 1992)

(methyl)penicillamine]N-methylamide;
and the salts, solvates, hydrates and prodrugs thereof.

11. A pharmaceutical composition comprising a compound according to any of Claims 1 to 10 and a pharmaceutical diluent, carrier or excipient.

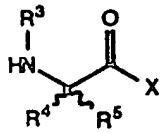
12. A process for preparing a compound of formula (1) as defined in Claim 1, which comprises

(a) coupling an acid of formula (2)



(2)

or an active derivative thereof, with an amine of formula (3),



(3)

followed by removal of any protecting groups; or

(b) interconverting a compound of formula (1), to another compound of formula (1).

C_{3-6}cycloalkyl or cycloalkenyl group, Het is -O-, $-S(O)_p-$ [where p is zero, or an integer 1 or 2] or $-N(R^{12})-$, and R^{11} is a hydrogen atom or an aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic, or hetero-aromatic group;

X is an amino ($-NH_2$), substituted amino, hydroxyl or substituted hydroxyl group, or is linked to the atom or group Het in R^5 to form a chain $-X-Alk-R^5-$ where X is $-N(R^{12})-$, Alk is an optionally substituted alkylene chain and R^5 is $-Het-C(R^9)(R^{10})-$;

and the salts, solvates, hydrates and prodrugs thereof.

2. A compound according to Claim 1 where R is a -CONHOH group.

3. A compound according to Claim 1 or 2 where R^1, R^3 and R^4 each represents a hydrogen atom.

4. A compound according to any of Claims 1 to 3 where R^2 represents a straight or branched C_{1-6}alkyl group.

5. A compound according to any of Claims 1 to 4 where R^9 and R^{10} is each an optionally substituted C_{1-6} alkyl group.

6. A compound according to Claim 5 where R^9 and R^{10} is each a methyl group.

7. A compound according to any of Claims 1 to 6 where Het is a sulphur atom.

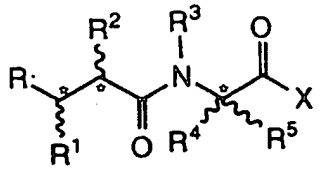
8. A compound according to any of Claims 1 to 7 where R^{11} is a hydrogen atom or a methyl group.

9. A compound according to any of Claims 1 to 8 where X is an amino or a N-methylamino group.

10. [4-(N-Hydroxyamino)-2(R)-3-(2-methylpropyl)succinyl]-L-[S-

CLAIMS

1. A compound of formula (1):



(1)

wherein R represents a -CONHOR^6 [where R^6 is a hydrogen atom or an acyl group], carboxyl (-CO_2H), esterified carboxyl, -SR^6 or -P(O)(X^{1}R^7) X^{2}R^8 group, where X^1 and X^2, which may be the same or different, is each an oxygen or sulphur atom and R^7 and R^8, which may be the same or different each represents a hydrogen atom or an optionally substitued alkyl, aryl, or aralkyl group;

R^1 represents a hydrogen atom or an optionally substituted alkyl, alkenyl, aryl, aralkyl, heteroaralkyl or heteroarylthioalkyl group;

R^2 represents an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, amino (-NH_2), substituted amino, carboxyl (-CO_2H), or esterified carboxyl group;

R^3 represents a hydrogen atom or an alkyl group;

R^4 represents a hydrogen atom or an alkyl group;

R^5 represents a group -C(R^9)(R^{10})Het-R^{11}, wherein R^9 and R^{10} which may be the same or different is each an optionally substituted alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R^{12})- groups (where R^{12} is a hydrogen atom or an optionally substituted alkyl group), or an optionally substituted cycloalkyl, cycloalkenyl, aryl or heteroaryl group, or R^9 and R^{10} together with the carbon atom to which they are attached ar link d together to form an optionally substituted

2.75 (3H, s); 2.40 (1H, dd); 2.15 (1H, dd); 1.50 (2H, m); 1.40 (3H, s); 1.35 (3H, s); 1.20 (1H, m); 0.90 (6H, 2d).

(methyl)penicillamin]-N-methylamide

A solution in anhydrous DMF (30ml) of 2-(R)-(2-methylpropyl)succinic acid-4-t-butyl monoester [2.9mmol; prepared from t-butylbromoacetate, BuLi and (S)-4-(phenylmethyl)-2-oxazolidinone according to the procedure of Intermediate 4 in WO93/24475], Intermediate 4 (2.93mmol), N-hydroxybenzotriazole (2.93mmol); N-methylmorpholine (8.79mmol), 1-(3-di-methylaminopropyl)-3-ethyl carbodiimide hydrochloride (3.19 mmol) and a trace amount of 4-dimethylaminopyridine was stirred at RT under an atmosphere of nitrogen for 18 hr. The reaction mixture was poured into 10% w/v aq.citric acid (100ml) and extracted into diethyl ether (100ml). The organic layer was washed with 10% w/v aq. $NaHCO_3$, separated, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica, eluting with 2-4% CH_3OH in CH_2Cl_2, to give the title compound.

b) [4-Hydroxy-2(R)-3-(2-methylpropyl]succinyl]-L-[S-(methyl)penicillamine]-N-methylamide

A solution of the compound of Example 1a (0.933mmol) in a mixture of TFA (10ml) and water (0.5ml) was left to stand at 4°C for 18 hr. The solvent was evaporated with the aid of a toluene/THF azeotrope to obtain the title compound.

c) [4-(N-Hydroxyamino)-2(R)-3-(2-methylpropyl]succinyl]-L-[S-(methyl)penicillamine]-N-methylamide

To a solution in anhydrous THF of the compound of Example 1b (0.933 mmol) at -20°C was added N-methylmorpholine (1.87 mmol), and ethyl chloroformate (1.12 mmol). After 1 hr, O-trimethylsilylhydroxylamine (3.75mmol) was added and the reaction mixture was allowed to warm to RT overnight. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and 10% w/v aq. citric acid. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified (SiO_2; 5-10% CH_3OH in CH_2Cl_2) to give the title compound. δ_H (CD_3OD) 4.50 (1H, s); 2.95 (1H, m);

33.5mmol), N-hydroxybenzotriazole (4.53g; 33.5mmol), methylamine hydrochloride (11.3g; 167.5 mmol); N-methylmorpholin (20.6ml; 184mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (7.1g; 36.9mmol) and a trace of 4-dimethylaminopyridine was stirred at RT under an atmosphere of nitrogen for 18 hr. The reaction mixture was poured into 10% w/v aq.citric acid (600ml) and extracted into diethyl ether (600ml). The organic layer was separated, washed with 10% w/v aq. $NaHCO_3$ solution (500ml), dried ($MgSO_4$) and evaporated. Following chromatography on silica, eluting with 20-50% ethyl acetate in hexane, the title compound was obtained as a clear glass (6.36g). δ_H ($CDCl_3$) 6.85 (1H, m); 5.75 (1H, d); 2.75 (3H, d); 2.50 (1H, br s); 1.50 (3H, s); 1.45 (9H, s); 1.35 (3H, s).

INTERMEDIATE 3

N-tert-butyloxycarbonyl-L-[S-(methyl)penicillamine]-N-methylamide

To a solution of Intermediate 2 (1g; 3.82mmol) in 2N aq. $NaOH/CH_3OH$ (10ml/30ml) was added iodomethane (1.18ml; 19mmol) in CH_3OH (4ml). After stirring at RT for 2 hr, the reaction mixture was concentrated to one quarter volume, then partitioned between diethyl ether and brine. The organic layer was washed with 10% w/v aq. citric acid, dried ($MgSO_4$) and evaporated to give the title compound (810mg) as a colourless glass. δ_H ($CDCl_3$) 6.80 (1H, m); 5.65 (1H, d); 4.20 (1H, d); 2.80 (3H, s); 2.10 (3H, s); 1.45 (9H, s); 1.40 (3H, s); 1.30 (3H, s).

INTERMEDIATE 4

L-[S-(Methyl)penicillamine]-N-methylamide trifluoroacetate

A solution of Intermediate 3 (810mg; 2.93mmol) in TFA/dichloromethane (10ml/10ml) was stirred at RT for 2 hr. The solvent was then removed under reduced pressure with the aid of a toluene/THF azeotrope. The title compound (855mg) was obtained as a yellow tinged glass in quantitative yield. δ_H ($CDCl_3$) 8.4 (3H, br s); 7.9 (1H, q); 4.20 (1H, s); 2.80 (3H, d); 2.0 (3H, s); 1.45 (3H, s); 1.35 (3H, s).

EXAMPLE 1

a) [4-t-Butoxy-2(R)-3-(2-methylpropyl)succinyl]-L-[S-

radioactivity measured for each test compound with a control value obtained by performing the same assay in the abs nce of a gelatinase inhibitor.

The ability of compounds of the invention to prevent tumour cell invasion may be demonstrated in a standard mouse model. Thus, briefly, nude mice may be inoculated with a tumour cell line showing gelatinase - dependent invasion and the ability of compounds according to the invention to reduce subsequent lung tumour colonisation may be evaluated in accordance with standard procedures. In out tests, compounds according to the invention, when administered orally in a single dose at 100mg/kg to mice in the above model have reduced lung tumour colonisation to negligable levels for periods of twelve hours duration or longer.

In general, compounds according to the invention are non-toxic at pharmaceutically useful doses. Thus, for example, when the compounds were administered to mice at the doses described above no adverse effects were observed.

INTERMEDIATE 1
N-tert-butoxycarbonyl-L-penicillamine

To a solution of L(+)- penicillamine (24g; 161mmol) in 10% w/v aqueous sodium carbonate solution (300ml) was added di-tert-butyl dicarbonate (35.1g; 161mmol) in tert-butanol (300ml). After stirring the reaction mixture for 18 hr at RT, the volume was reduced by approximately one half under reduced pressure and the pH was adjusted to 2 using 1N hydrochloric acid. The resulting slurry was extracted several times with diethyl ether, the ethereal layers being combined, dried ($MgSO_4$) and evaporated to give the title compound (36.7g) as a clear gum. δ_H ($CDCl_3$) 8.65 (1H, br s); 5.50 (1H, d), 4.35 (1H, d); 2.00 (1H, br s); 1.60 (3H, s); 1.50 (9H, s); 1.45 (3H, s).

INTERMEDIATE 2
N-tert-butoxycarbonyl-L-penicillamine-N-methylamide

A solution in anhydrous DMF (250ml) of Intermediate 1 (11.69g;

initial rate in the presence of inhibitor, [E] is th total enzyme concentration and [I] the total inhibitor concentration in the reaction mixture.

For stromelysin and collagenase, K_i (app) was assumed to approximate to the true K_i as [S] << K_m for the substrate hydrolysis. For gelatinase the K_i was determined by performing the analyses at several substrate concentrations. A plot of K_i(app) vs. [S] then gave the true K_i as the value of the y-axis intercept.

The following results were obtained with the compound of Example 1c):

	KI(nM)	
Collagenase	Stromelysin-1	Gelatinase-72kD
2.9	90.0	1.55

EXAMPLE B

The oral activity of the compounds according to the invention may be determined using the mouse pleural cavity assay described below. This assay measures the ability of compounds of the invention when administered orally to inhibit a subsequent inoculation of gelatinase into the mouse pleural cavity.

A 2ml solution of the test compound (for example around 25µm/kg) in an appropriate solvent (e.g. 50% polyethylene glycol (PG)) plus a variable proportion of dimethyl sulphoxide (DMSO) (if required) is administered orally. After an interval of up to 24 hrs, 0.4ml of a mixture of an equal volume (2.2ml) of the enzyme gelatinase A (72K form at a concentration of 20nM) and radiolabelled [^{14}C]-gelatin (at an approximate concentration of 10µM i.e. 500 times molar excess) is injected into the pleural cavity and maintained at 4°C. After 35 min mice are overdosed with anaesthetic, the contents of the pleural cavity aspirated and the aspirates cleared by centrifugation at 4°C then diluted to 15% in trichloroacetic acid (TCA) and left overnight at 4°C. The resulting TCA precipitate is then separated by centrifugation and radioactivity in each supernatant measured by scintillation counting. Results are expressed as a % inhibition of enzyme activity calculated by comparing the

In the Examples, the following abbreviations are used:

RT	-	room temperature
DMF	-	dimethylformamide
THF	-	tetrahydrofuran
TFA	-	trifluoroacetic acid

EXAMPLE A

The activity of the compounds of the invention may be determined as described below.

All enzyme assays to determine Ki values were performed using the peptide substrate Dnp-Pro-Leu-Gly-Leu-Trp-Ala-D-Arg-NH_2. [M. Sharon Stock and Robert D. Gray. JBC 264, 4277-81, 1989]. The enzymes cleave at the Gly-Leu bond which can be followed fluorimetrically by measuring the increase in Trp fluorescence emission associated with the removal of the quenching dinitrophenol (Dnp) group.

Essentially, enzyme (e.g. gelatinase, stromelysin, collagenase) at 0.08-2nM; a range of inhibitor concentrations (0.1-50 x Ki) and substrate (approx. 20μm) are incubated overnight in 0.1M Tris/HCl buffer, pH 7.5, containing 0.1M NaCl, 10mM $CaCl_2$ and 0.05%. Brij 35 at either room temperature or 37°C depending on the enzyme. The reaction is stopped by adjusting the pH to 4 using 0.1M sodium acetate buffer and the fluorescence read at an excitation wavelength of 280nm and emission wavelength of 346nm.

K_i values can be established using the equation for tight-binding inhibition:-

$$V_i = \frac{V_o}{2[E]}\left(\sqrt{(K_{i(app)} + [I])^2 + 2(K_{i(app)} - [I])[E] + [E]^2} - (K_{i(app)} + [I] - [E])\right)$$

where V_o is the initial rate of reaction in the absence of inhibitor, V_i is the

constitution with a suitable vehicle, e.g. sterile pyrog n-free wat r, before use.

The compounds of formula (1) may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation the compounds for use according to the present invention are conventiently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichloro-difluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispenser device may be accompanied by instructions for administration.

The doses of compounds of formula (1) used in the above applications will vary depending on the disease or disorder and condition of the patient to be treated but in general may be in the range around 0.5mg to 100mg/kg body weight, particularly from about 1mg to 50mg/kg body weight. Dosage units may be varied according to the route of administration of the compound in accordance with conventional practice.

DESCRIPTIONS OF SPECIFIC EMBODIMENTS

The invention is further illustrated in the following non-limiting Examples.

Compounds for use according to the present invention may be formulated for oral, buccal, parental or rectal administration or in a form suitable for nasal administration or administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles; and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (1) may be formulated for parental administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for

such as rheumatoid arthritis, osteoarthritis and septic arthritis, and to be of use to prevent tumour cell metastasis and invasion. The compounds may therefore be of use in the treatment of cancer, particularly in conjunction with radiotherapy, chemotherapy or surgery, or in patients presenting with primary tumours, to control the development of tumour metastasis. Particular cancers may include breast, melanoma, lung, head, neck or bladder cancers. Other uses to which the compounds of the invention may be put, include use for prevention of myelin degradation in the central and peripheral nervous system, for example in the treatment of multiple sclerosis, use for controlling peridontal diseases such as gingivitis, and use in tissue remodelling.

The compounds according to the invention can also be expected to be of use in the prophylaxis or treatment of angiogenic diseases. Such diseases may be characterised by the pathological growth or new capillaries [see, for example Folkman, J. and Klagsbrun, M. Science 235, 442-447 (1987) and Moses, M. A. and Langer, R. Bio/Technology 9, 630-634 (1991)]. Particular angiogenesis dependent diseases include solid tumours and arthritic diseases as described above, and, additionally, psoriasis, eye diseases such as the proliferative reinopathies, neovascular glaucome and ocular tumours, angiofibromas, and hemangiomas.

For use in the above applications, the compounds of formula (1) may be formulated in a conventional manner, optionally with one or more physiologically acceptable carriers, diluents or excipients.

Thus according to a further aspect of the invention we provide a pharmaceutical composition comprising a compound of formula (1) and a pharmaceutically acceptable diluent, carrier or excipient.

In a still further aspect the invention provides a process for the production of a pharmaceutical composition comprising bringing a compound of formula (1) into association with a pharmaceutically acceptable diluent, carrier or excipient.

alkali metal hydroxide such as lithium hydroxide in a solvent such as an aqueous alcohol, e.g. aqueous methanol, or by treatment with an acid such as a mineral acid, e.g. hydrochloric acid in the presence of a solvent, e.g. dioxane.

Similarly esters of formula (1), for example where R is a CO_2R^{13} group and/or X contains a $-CO_2R^{13}$ group may be prepared by reaction of the corresponding acids, where R is a $-CO_2H$ group and/or X contains a $-CO_2H$ group or an active derivative thereof, with an alcohol $R^{13}OH$ using standard conditions.

In another interconversion process, a compound of formula (1) wherein R^5 is a group $-C(R^9)(R^{10})S-R^{11}$ may be oxidised to a corresponding compound where R^5 is a group $-C(R^9)(R^{10})SOR^{11}$ or $-C(R^9)(R^{10})SO_2R^{11}$ using an oxidising agent, for example a peroxymonosulphate such as potassium peroxymonosulphate, in a solvent such as an aqueous alcohol at ambient temperature or a peroxyacid in a halogenated hydrocarbon solvent such as dichloromethane at a low temperature, e.g. around -78°C.

The compounds according to the invention are potent inhibitors of the metalloproteinases collagenase, stromelysin and gelatinase and advantageously have a long duration of action when administered orally. The activity of the compounds may be determined by the use of appropriate enzyme inhibition tests for example as described in Example A hereinafter or by oral administration to mice as described hereinafter in Example B. In our tests using this approach, compounds according to the invention have been shown to inhibit stromelysin, and, in particular, collagenase and gelatinase with Ki values in the nanomolar range.

The compounds according to the invention can be expected to be of use in the prophylaxis or treatment of diseases or disorders in which stromelysin, collagenase and gelatinase have a role. Thus for example the compounds of formula (1) may be of use in the prophylaxis or treatment of musculo-skeletal disorders, for example arthritic diseases

The compounds of formula (8) may be prepared by reaction of an acyl halide $RCH_2CH(R^2)COHal$ (where Hal is a halogen atom such as a chlorine, bromine or iodine atom) with a solution of (S)-4-(phenylmethyl)-2-oxazolidinone in the presence of a base such as n-butyllithium in a solvent such as tetrahydrofuran at a low temperature, e.g. around -78°C.

Acyl halides $RCH_2CH(R^2)COHal$ may be prepared by treatment of the corresponding known acids $RCH_2CH(R^2)CO_2H$ with conventional halogenating agents for example thionyl halides under standard reaction conditions.

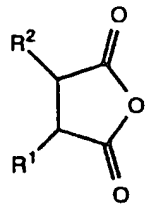
Intermediates of formula (3) are either known compounds or may be prepared from known amino acid starting materials using standard methods, for example by employing a series of substitution reactions to manipulate the groups R^5 and X as described in the Examples hereinafter, or for example as described by Wessjohann *et al*, Chem. Ber. 1992, 125, 867-882.

Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1). Thus, for example, a compound of formula (1) wherein R is a $-CONHOR^6$ group may be prepared by reaction of a corresponding acid of formula (1) wherein R is a $-CO_2H$ group or an active derivate thereof (for example an acid chloride or an acid anhydride) with hydroxylamine or an O-protected derivative or a salt thereof or a reagent R^6ONH_2 where R^6 is an acyl group. The reaction may be performed using the reagents and conditions described above in the preparation of compounds of formula (1) from the starting materials of formulae (2) and (3).

In another interconversion process, compounds of formula (1) wherein R is $-CO_2H$ and/or X contains a $-CO_2H$ group may be prepared by hydrolysis of the corresponding esterified compounds (for example where R is a $-CO_2R^{13}$group and/or X contains a similar group) using conventional procedures, for example by treatment with a base, e.g. an

for use in the above reactions are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

Intermediate acids of formula (2) wherein R is a -CONHOR^6 group or a protected derivative thereof may be prepared by reaction of an anhydride of formula (7)

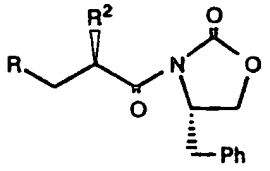


(7)

with a hydroxylamine such as O-benzylhydroxylamine or NH_2OR^6 where R^6 is an acyl group in a solvent such as tetrahydrofuran at a low temperature, e.g. around -20°C, followed where desired by removal of the protecting group as described above.

The intermediate anhydrides of formula (7) may be prepared for example by heating for example at the reflux temperature, a diacid of formula (5) where R is -CO_2H with an acyl chloride such as acetyl chloride.

The homochiral acids of formula (2a) may be prepared according to another feature of the invention by oxidation of an oxazolidinone of formula (8)



(8)

(where Ph is a phenyl group)

using an oxidising agent such as peroxide, e.g. hydrogen peroxide in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a low temperature, e.g. around 0°C followed by treatment with a base, such as lithium hydroxid , at an elevated temperature.

hydrolysis of the corresponding di-ester $R^{19}OOCCH(R^2)COOR^{19}$ using a base, for example an alkali hydroxide, in an inert solvent such as dioxane at a low temperature e.g. around 0°C. The di-esters for use in this reaction may be prepared by alkylation of the corresponding malonates of formula $R^{19}OOCCH_2COOR^{19}$ with a halide R^2Hal [where Hal is a halogen atom such as a chlorine or bromine atom] in the presence of a base, e.g. a hydride such as sodium hydride in a solvent such as tetrahydrofuran at ambient temperature. Malonates of formula $R^{19}OOCCH_2COOR^{19}$ are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

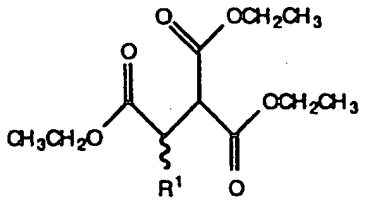
Intermediate phosphites of formula $P(OR^{20})(X^1R^7)X^2R^8$ may be prepared by reaction of a phosphite $HP(O)(X^1R^7)X^2R^8$ with an appropriate amine $(R^{20})_2NH$ e.g. a silazane, at an elevated temperature, e.g. the reflux temperature. Phosphites of formula $HP(O)(X^1R^7)X^2R^8$ are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

Intermediates of formula (4) where R is a $-SR^6$ group are either known compounds or may be prepared from known starting materials of formula $R^6SCH(R^1)CH(CO_2CH_2CH_3)_2$ by using a similar series of reactions to those just described for the preparation of compounds of formula (4) where R is a carboxyl group.

In another process, intermediate acids of formula (2) wherein R is a $-P(O)(X^1R^7)X^2R^8$ group may be prepared by reaction of an acid $R^2CH_2CO_2H$ with a phosphonate $P(O)(X^1R^7)(X^2R^8)CH_2OR^{21}$ where R^{21} is a leaving group, for example a trifluoromethylsulphonyloxy group in the presence of a base such as n-butyllithium in a solvent such as tetrahydrofuran. Phosphonates for use in this reaction may be prepared from the corresponding compound $P(O)(X^1R^7)(X^2R^8)CH_2OH$ by reaction with paraformaldehyde in the presence of a base such as triethylamine at an elevated temperature followed by reaction with a halide $R^{21}Hal$ in the presence of a base such as sodium hydride in a solvent such as an ether. Phosphonates $P(O)(X^1R^7)(X^2R^8)CH_2OH$ and acids $R^2CH_2CO_2H$

using an appropriate acyl halide, for example an acyl chloride in a solvent such as an alcohol, e.g. methanol at a low temperature, e.g. around O°C.

Acids of formula (5) may be prepared by alkylation of a compound of formula (6)



(6)

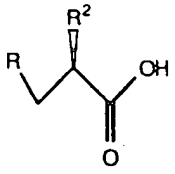
with an appropriate halide, e.g. a compound R^2Hal, where Hal is a halogen atom such as a chlorine or bromine atom in the presence of a base, for example an alkoxide such as sodium ethoxide in a solvent such as an alcohol, e.g. ethanol at ambient temperature, followed by decarboxylation using for example concentrated hydrochloric acid at an elevated temperature,e.g. the reflux temperature.

Intermediates of formula (6) are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

Intermediate esters of formula (4) where R is a $-P(O)(X^1R^7)X^2R^8$ group may be prepared by reaction of an acrylate $R^1CHC(R^2)COR^{19}$ with a phosphite:$P(OR^{20})(X^1R^7)X^2R^8$ [where R^{20} is a leaving group, for example a silyl group such as a trialkylsilyl group e.g. a trimethylsilyl group] at an elevated temperature.

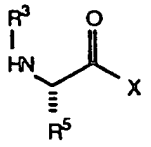
Acrylates of formula $R^1CHC(R^2)COR^{19}$ may be prepared by reaction of a mono-ester $HOOCCH(R^2)COOR^{19}$ with an aldehyde R^1CHO or a polymer thereof e.g. paraformaldehyde or paraldehyde in the presence of a base, for example an organic base such as piperidine. The reaction may be performed in a solvent, such as pyridine, optionally at an elevated temperature.

Mono-esters of formula $HOOCCH(R^2)COOR^{19}$ may be prepared by



(2a)

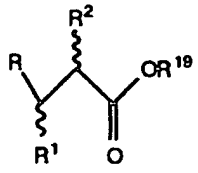
with an amine of formula (3a)



(3a)

as described above

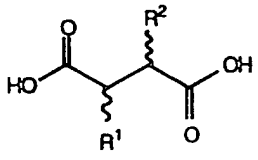
Intermediate acids of formula (2) wherein R is a carboxyl or esterified carboxyl group or a group $-P(O)(X^1R^7)X^2R^8$ or $-SR^6$ may be prepared from a corresponding ester of formula (4)



(4)

where R^{19} is an alkyl group, for example a methyl or t-butyl group, using for example trifluoroacetic acid, or, when R^{19} is an aralkyl group, such as a benzyl group, by hydrogenolysis, for example by reaction with hydrogen in the presence of a metal catalyst, e.g. palladium, on a support such as carbon in a solvent such as an alcohol, e.g. methanol optionally at an elevated pressure and temperature.

An ester of formula (4) where R is a carboxyl or esterified carboxyl group may be prepared by esterification of the corresponding acid of formula (5)



(5)

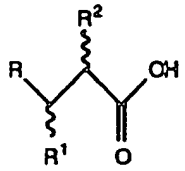
ether, e.g. a cyclic ether such as tetrahydrofuran, an amide e.g. a substituted amide such as dimethylformamide, or a halogenated hydrocarbon such as dichloromethane at a low temperature, e.g. -30°C to ambient temperature, such as -20°C to 0°C, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine or a cyclic amine such as N-methylmorpholine. Where an acid of formula (2) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as N,N'-dicyclohexylcarbodiimide, or 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide, advantageously in the presence of a triazole such as 2-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate for example ethylchloroformate, prior to reaction with the amine of formula (3).

Free hydroxyl or carboxyl groups in the starting materials of formulae (2) [where R is -CONHOH or CO_2H] and (3) may need to be protected during the coupling reaction. Suitable protecting groups and methods for their removal may be those mentioned above. Where R in the intermediates of formula (2) is a $-P(O)(X^1R^7)X^2R^8$ group, at least one of R^7 or R^8 is other than a hydrogen atom. Conveniently, each of R^7 and R^8 is an optionally substituted alkyl, aryl or aralkyl group. Such groups, when present in compounds of the invention may be cleaved as described below to yield other compounds of the invention wherein R^7 and/or R^8 is each a hydrogen atom.

It will be appreciated that where a particular stereoisomer of formula (1) is required, this may be obtained by resolution of a mixture of isomers following the coupling reaction of an acid of formula (2) and an amine of formula (3). Conventional resolution techniques may be used, for example separation of isomers by chromatography e.g. by use of high performance liquid chrormatography. Where desired, however, appropriate homochiral starting materials may be used in the coupling reaction to yield a particular stereoisomer of formula (1). Thus, in particular process a compound of formula (1a) may be prepared by reaction of a compound of formula (2a)

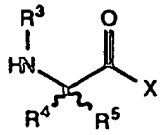
particular reaction. Suitable amino or hydroxyl protecting groups include benzyl, benzyloxycarbonyl or t-butyloxycarbonyl groups. These may be removed from a protected derivative by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an alcohol e.g. methanol, or by treatment with trimethylsilyl iodide or trifluoroacetic acid in an aqueous solvent. Suitable carboxyl protecting groups include benzyl groups, which may be removed from a protected derivative by the methods just discussed, or alkyl groups, such as a t-butyl group which may be removed from a protected derivative by treatment with trifluoroacetic acid in an aqueous solvent. Other suitable protecting groups and methods for their use will be readily apparent. The formation of the protected amino, hydroxyl or carboxyl group may be achieved using standard alkylation or esterification procedures, for example as described below.

Thus according to a further aspect of the invention a compound of formula (1) may be prepared by coupling an acid of formula (2)



(2)

or an active derivative thereof, with an amine of formula (3)



(3)

followed by removal of any protecting groups.

Active derivatives of acids for formula (2) include for example acid anhydrides, or acid halides, such as acid chlorides.

The coupling reaction may be performed using standard conditions for amination reactions of this type. Thus, for example the reaction may be achieved in a solvent, for example an inert organic solvent such as an

In a still further useful group of compounds of formula (1a), R is a -CONHOH, $-CO_2H$ or $-P(O)(OH)_2$ group, R^2 is an isobutyl group, R^5 is a group $-C(CH_3)_2SR^{11}$ where R^{11} is a hydrogen atom or an optionally substitued C_{1-6} alkyl group, and X is an amino ($-NH_2$) or $-NHR^{18}$ group where R^{18} is an optionally substituted C_{1-6} alkyl group. Compounds of this type wherein R is a -CONHOH group are particularly useful; as are those compounds wherein R^{11} is a hydrogen atom or a methyl group; and those compounds wherein R^{18} is a hydrogen atom or a methyl group.

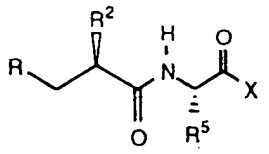
One further group of compounds according to the invention has the formula (1a) wherein R and R^2 are as defined for formula (1), R^5 is a group $-C(CH_3)_2SH$ or $-C(CH_3)_2SCH_3$ and X is $-NH_2$ or $-NHCH_3$. Particularly useful compounds of this type are those wherein R is a group -CONHOH, $-CO_2H$ or $-P(O)(OH)_2$ and R^2 is a C_{3-6}alkyl group. Particularly useful compounds are those where R^2 is an isobutyl group.

In compounds of the above described types, R^5 is preferably a group $-C(CH_3)_2SCH_3$. In these compounds, R is preferably $-CO_2H$ or $-P(O)(OH_2)$ or is especially -CONHOH. X is preferably $-NH_2$ or $-NHCH_3$.

An important compound according to the invention is:

[4-(N-Hydroxyamino)-2(R)-3-(2-methylpropyl)succinyl]-L-[S-(methyl) penicillamine] N-methylamide; and the salts, solvates, hydrates and prodrugs thereof.

The compounds according to the invention may be prepared by the following general processes, more specifically described in the Examples hereinafter. In the description and formulae below the groups R, R^1, R^2, R^3, R^4, R^5 and X are as defined above, except where otherwise indicated. It will be appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a



(1a)

wherein R, R^2, R^5 and X are as defined for formula (1); and the salts, solvates, hydrates and prodrugs thereof.

A particularly useful group of compounds of formula (1a) are those wherein R represents a -CONHOH, $-CO_2H$ or $-P(O)(OH)_2$ group; R^2 and R^5 are as defined for formula (1); X is an amino ($-NH_2$) or substituted amino group; and the salts, solvates, hydrates and prodrugs thereof.

Particularly useful compounds of formula (1a) are those wherein R^5 is a group $-C(R^9)(R^{10})S(O)pR^{11}$. Compounds of this type in which R^5 is a $-C(R^9)(R^{10})SR^{11}$ group are especially useful.

Other useful compounds of formula (1a) include those wherein R^2 represents a C_{3-6}alkyl group, particularly an isobutyl or n-pentyl group, or a cycloalkylC_{3-6}alkyl group, particularly a cyclohexylpropyl, cyclohexylbutyl or cyclohexylpentyl group.

In the compounds of formula (1a) X may be a $-NH_2$ group or a group $-NR^{17}R^{18}$ as defined for compounds of formula (1), particularly a $-NHR^{18}$ group.

An especially useful group of compounds according to the invention has the formula (1a) wherein R^2 is a C_{3-6}alkyl group, R^5 is a group $-C(R^9)(R^{10})SR^{11}$ where R^9 and R^{10} is each the same and is each an optionally substituted C_{1-6} alkyl group, and R^{11} is as defined for formula (1); and X is an amino ($-NH_2$) or $-NHR^{18}$ group, particularly where R^{18} is an optionally substituted C_{1-6} alkyl group. Compounds of this type wherein R^5 is a group $-C(CH_3)_2SR^{11}$ are particularly useful, especially where the group R^{11} is a hydrogen atom or an optionally substituted saturated C_{1-6} alkyl chain. In compounds of this last type X is preferably an amino ($-NH_2$) group or a $-NHCH_3$ group.

heterocycloaliphatic, aromatic or heteroaromatic group as described above for compounds of formula (1).

The group X in compounds of formula (1) may be in particular an amino ($-NH_2$) or $-NR^{17}R^{18}$ group. Particular $-NR^{17}R^{18}$ groups are $-NHR^{18}$ groups. Groups of this type include those where R^{18} is a C_{1-6}alkyl group, for example a methyl, ethyl, or n-propyl group, optionally interrupted by one or more -O- or -S- atoms or $-N(R^{12})$ [e.g. -NH- or $-N(CH_3)-$] or aminocarbonyloxy groups and optionally substituted by a hydroxyl, carboxyl, carboxyalkyl, e.g. carboxymethyl, carboxamido, amino, $-NR^{17}R^{18}$, [for example di-C_{1-6}alkylamino such as dimethylamino, C_{1-6}alkylamino such as methylamino, or C_{3-6} cyclic amino such as morpholinyl, pyrrolidinyl or pyridinyl] or phenyl optionally substituted by one, two or more R^{16} substituents.

A particularly useful group of compounds according to the invention is that of formula (1) wherein R^5 is a group $-C(R^9)(R^{10})Het-R^{11}$ where Het is -S(O)p and R^9, R^{10} and R^{11} are as defined for formula (1). Compounds of this type wherein Het is -S- are particularly useful.

A further particularly useful group of compounds of formula (1) are those wherein X is an amino or substituted amino group. Particularly useful compounds of this type are those wherein X is $-NHCH_3$ or, especially, $-NH_2-$.

In general, in compounds of formula (1) the groups R^1, R^3 and R^4 is each preferably a hydrogen atom.

In a further preference, the group R in compounds according to the invention is a -CONHOH or a $-CO_2H$ group or a metabolically labile ester thereof, or a group $P(O)(OH)OR^8$. In a particular preference, however, R is a $-CO_2H$, $-P(O)(OH)_2$ or, especially, a -CONHOH group.

An especially useful group of compounds according to the invention has the formula (1a)

When the group R in compounds of formula (1) is a $-P(O)(X^1R^7)X^2R^8$ group it may in particular be a $P(O)(OR^7)OR^8$, e.g. a $-P(O)(OH)OR^8$ group, or a $-P(O)(SH)OR^8$ or $-P(O)(OH)SR^8$ group. Examples of such groups include $-P(O)(OCH_3)OCH_3$, $-P(O)(OCH_2CH_3)OCH_2CH_3$, -P(O)(OH)OH, -P(O)(OH)SH, -P(O)(SH)OH, $-P(O)(OH)OCH_3$, $-P(O)(OH)SCH_3$, $-P(O)(OH)OCH_2CH_3$, -P(O)(OH)OPh, -P(O)(OH)SPh, $-P(O)(OH)OCH_2Ph$ or $-P(O)(OH)SCH_2Ph$, where Ph is a phenyl group optionally substituted by one or more substituents R^{16}.

In the compounds of formula (1) the group R^1 may in particular be a C_{1-6}alkyl group such as a methyl group, an aralkyl group such as benzyl group, an arylthioalkyl group such as a phenylthiomethyl group or a heteroarylthioalkyl group such as thienylthiomethyl, pyridinylthiomethyl or pyrimidinylthiomethyl group or is especially a hydrogen atom.

The group R^2 in compounds of formula (1) may be in particular an optionally substituted C_{1-6}alkyl, C_{3-8}cycloalkyl, or C_{6-12}aryl group. Particular types of these groups are optionally substituted C_{3-6}alkyl, such as n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl or i-pentyl; cyclopentyl; cyclohexyl; phenyl; 1- or 2-naphthyl. Each of these cycloalkyl or aryl groups may be substituted, by one, two or more substituents R^{16} described above.

The groups R^3 and R^4 in compounds of formula (1) may each in particular be a methyl group, or, especially, a hydrogen atom.

The group R^5 in compounds of formula (1) may in particular be a group $-C(R^9)(R^{10})Het\text{-}R^{11}$ where R^9 and R^{10} are the same. Particular compounds of this type are those wherein R^9 and R^{10} is each the same and is each an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl group.

In another group of compounds of formula (1) the group R^5 may be a group $-C(R^9)(R^{10})Het\text{-}R^{11}$ where R^{11} is an aliphatic, cycloaliphatic,

atom.

When X is linked to the atom or group Het in R^5 to form a chain -X-Alk-R^5, the optionally substituted alkylene chain represented by Alk may be an optionally substituted straight or branched C_{2-9} alkylene chain, for example an ethylene, propylene or butylene chain. Optional substituents present on the alkylene chain include those described above in relation to the alkyl group represented by R^2. In compounds of this type, the group X is -N(R^{12})-, where R^{12} is as defined above. The group R^5 is -Het-C(R^9)(R^{10})- where Het, R^9 and R^{10} are as defined above.

Salts of compounds of formula (1) include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids; such as hydrochlorides, hydrobromides, hydroiodides, p-toluene sulphonates, phosphates, sulphates, perchlorates, acetates, trifluoro-acetates, propionates, citrates, malonates, succinates, lactates, oxalates, tartarates and benzoates.

Salts may also be formed with bases. Such salts include salts derived from inorganic or organic bases, for example alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Prodrugs of compounds of formula (1) include those compounds, for example esters, alcohols or amines, which are convertible, *in vivo*, by metabolic means, e.g. by hydrolysis, reduction, oxidation or transesterification, to compounds of formula (1).

When the group R in compounds of the invention is an esterified carboxyl group, it may be a metabolically labile ester of formula -CO_2R^{13} where R^{13} may be an ethyl, benzyl, phenylethyl, phenylpropyl, 1- or 2-naphthyl, 2,4-dimethylphenyl, 4-t-butylphenyl, 2,2,2-trifluoroethyl, 1-(benzyloxy)benzyl, 1-(benzyloxy)ethyl, 2-methyl-1-propionyloxypropyl, 2,4,6-trimethylbenzoyloxymethyl or pivaloyloxymethyl group.

substituents. The heteroaromatic group may be connected to the remainder of the compound of formula (1) through any ring carbon atom, or where appropriate through a heteroatom or group -N(R^{12})-.

When X in the compounds of formula (1) represents a substituted amino group it may be for example a group of formula -N$R^{17}R^{18}$, where R^{17} and R^{18}, which may be the same or different, is each a hydrogen atom (with the proviso that when one of R^{17} or R^{18} is a hydrogen atom, the other is not) or an optionally substituted straight or branched alkyl group, optionally interrupted by one or more -O- or -S- atoms or -N(R^{12})- or aminocarbonyloxy [-NHC(O)O-] groups or R^{17} and R^{18}, together with the nitrogen atom to which they are attached, may form an optionally substituted C_{3-6}cyclic amino group optionally possessing one or more other heteroatoms selected from -O- or -S-, or -N(R^{12})- groups.

When R^{17} and/or R^{18} is an alkyl group it may be for example a C_{1-6}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl group, optionally interrupted by one or more -O- or -S- atoms, or -N(R^{13})- or aminocarbonyloxy groups and may be for example a methoxymethyl, ethoxymethyl, ethoxymethyl, ethoxyethyl or ethylamino-carbonyloxymethyl group. The optional substituents which may be present on such groups include hydroxyl (-OH), carboxyl (-CO_2H), esterified carboxyl (-CO_2R^{13}), carboxamido (-$CONH_2$), substituted carboxamido, e.g. a group -CON$R^{17}R^{18}$ where N$R^{17}R^{18}$ is as defined herein, amino (-NH_2), substituted amino, for example a group of formula -N$R^{17}R^{18}$, aminosulphonylamino, for example -N(R^{12})SO_2NH_2 or -N(R^{12})SO_2N$R^{17}R^{18}$ or aryl, e.g. C_{6-12} aryl such as phenyl, optionally substituted by one, two or more R^{16} substituents selected from those listed above.

Particular examples of cyclic amino groups represented by -N$R^{17}R^{18}$ include morpholinyl, imidazolyl, piperazinyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, pyrrolidinyl, pyridinyl and pyrimidinyl groups.

When the group X is a substituted hydroxyl group it may be for example a group -OR^{11} where R^{11} is as defined above, other than a hydrogen

may be present on groups of these types include one or more amino ($-NH_2$), substituted amino [for example a group $-NR^{17}R^{18}$ as described below in relation to the group X], C_{6-12}aryl, e.g. optionally substituted phenyl, C_{6-12}aryloxy e.g. optionally substituted phenoxy, [the optional substituents in each case being R^{16} groups as defined above] C_{3-8}cycloalkyl, e.g. cyclopentyl or cyclohexyl, C_{3-8}cycloalkoxy, e.g. cyclopentyloxy or cyclohexyloxy, carboxyl ($-CO_2H$) or $-CO_2R^{13}$ groups.

Cycloaliphatic groups represented by R^{11} in compounds of formula (1) include optionally substituted C_{3-8}cycloalkyl and C_{3-8}cycloalkenyl groups, for example optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl and cyclohexenyl groups. Optional substituents include those groups R^{16} described above.

Heterocycloaliphatic groups represented by R^{11} in the compounds of formula (1) include optionally substituted C_{5-7}heterocycloalkyl groups containing one or two heteroatoms selected from -O- or -S-, or a group $-N(R^{12})-$, for example optionally substituted piperazinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, or N-methylpiperidinyl groups. Optional substituents include those groups R^{16} described above. The heterocycloalkyl groups represented by R^{11} may be attached to the remainder of the molecule through any ring carbon atom.

When the group R^{11} in compounds of formula (1) is an aromatic group it may be for example an optionally substituted mono- or bicyclic C_{6-12}aryl group, for example an optionally substituted phenyl or 1- or 2-naphthyl group. Optional substituents which may be present on groups of this type include those R^{16} substituents described above.

Heteroaromatic groups represented by the group R^{11} include mono-or bicyclic C_{5-9}heteroaromatic groups containing one, two or three heteroatoms selected from -O- or -S-, or $-N(R^{12})$ groups. Particular examples include pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, 1-indolyl, 2-indolyl, 1-quinolinyl or 2-quinolinyl groups. Such groups may be optionally substituted, for example by one or more R^{16}

such as methyl or ethyl groups.

When the group R^9 or R^{10} in compounds of formula (1) is an optionally substituted alkyl or alkenyl group it may be a straight or branched C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl i-propyl, n-butyl, i-butyl, n-pentyl or n-hexyl or C_{2-6}alkenyl e.g. ethenyl or 1-propenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R^{12})- groups where R^{12} is a hydrogen atom or an optionally substituted C_{1-6}alkyl group such as a methyl, ethyl or propyl group.

Optional substituents which may be present on such groups include one or more C_{1-6}alkoxy, C_{1-6}alkylthio, C_{6-12}arylC_{1-6}alkoxy, aralkylthio, amino, substituted amino, carboxyl, -CO_2R^{13}, aryl or heteroaryl groups as defined above in connection with the group R^1, or an optionally substituted cycloalkyl or cycloalkenyl group as defined below in connection with the groups R^9 and R^{10}.

When the group R^9, R^{10} or R^9 and R^{10} together with the carbon atom to which they are attached, is an optionally substituted cycloalkyl or cycloalkenyl group, it may be for example a C_{3-8}cycloalkyl, e.g. cyclopropyl, cyclopentyl or cyclohexyl, or C_{3-8}cycloalkenyl e.g. cyclopropenyl, cyclopentenyl or cyclohexenyl, group optionally substituted by one, two or more C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkoxy, e.g. methoxy or ethoxy, C_{1-6}alkylthio, e.g. methylthio, or hydroxyl groups.

The term Het in compounds of formula (1) may represent -O-, -S-, -S(O)-, -$S(O)_2$- or -N(R^{12})- where R^{12} is a hydrogen atom or a C_{1-6}alkyl group as defined above.

When R^{11} in compounds of formula (1) is an aliphatic group it may be for example an optionally substituted saturated or unsaturated straight or branched C_{1-6}alkyl chain optionally interrupted by one or more -O- or -S- atoms or groups selected from -N(R^{12})-, -CO-, -CON(R^{12})-, or -N(R^{12})CO-. Particular groups include optionally substituted methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, ethenyl, 1-propenyl, 1-butenyl or 2-butenyl groups. Optional substituents which

cyclopentylpropyl, cyclopentylbutyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, or cyclohexylbutyl group.

Optional substituents which may be present on aryl, aralkyl, heteroaralkyl or heteroarylthioalkyl groups represented by R^1 or R^2 include those R^{16} substituents discussed below.

The aryl, aralkyl, heteroaryl, heteroaralkyl or heteroarylthioalkyl groups represented by R^1 and/or R^2 in compounds of formula (1) may each optionally be substituted in the cyclic part of the group by one, two or more substituents [R^{16}] selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkoxy e.g. methoxy or ethoxy, C_{2-6}alkylenedioxy, e.g. ethylenedioxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, amino ($-NH_2$), nitro, cyano, hydroxyl (-OH), carboxyl ($-CO_2H$), $-CO_2R^{13}$, where R^{13} is as defined above, C_{1-6}alkylcarbonyl, e.g. acetyl, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6} alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylamino-sulphonyl e.g. dimethylaminosulphonyl or diethylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, sulphonylamino ($-NHSO_2H$), C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, or C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino groups. It will be appreciated that where two or more R^{16} substituents are present, these need not necessarily be the same atoms and/or groups. The R^{16} substituents may be present at any ring carbon atom away from that attached to the rest of the molecule of formula (1). Thus, for example, in phenyl groups any substituents may be present at the 2-, 3-, 4-, 5- or 6- positions relative to the ring carbon atom attached to the remainder of the molecule.

When the groups R^3 and R^4 in compounds of formula (1) are alkyl groups, they may be for example straight or branch d C_{1-6}alkyl groups

naphthylpropyl, naphthylbutyl or naphthylpentyl groups.

When the group R^1 in compounds of formula (1) is a heteroaralkyl group, it may be for example an optionally substituted mono-or bicyclic C_{3-9}heteroarylC_{1-6}alkyl group, such as an optionally substituted pyrrolylmethyl, furanylmethyl, thienylmethyl, imidazolylmethyl, oxazolylmethyl, thiazolylmethyl, pyrazolylmethyl, pyridinylmethyl, or pyrimidinylmethyl group.

Heteroarylthioalkyl groups represented by R^1 include optionally substituted mono- or bicyclic C_{3-9}heteroarylthioC_{1-6}alkyl groups such as optionally substituted pyrrolylthiomethyl, furanylthiomethyl, oxazolylthiomethyl, thiazolylthiomethyl, pyrazolylthiomethyl, pyridinylthiomethyl, or pyrimidinylthiomethyl groups.

When the group R^2 in compounds of formula (1) represents an alkyl or alkenyl group it may be for example a straight or branched C_{1-6}alkyl, or C_{2-6}alkenyl group, such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, ethenyl, 1-propenyl, 1-butenyl, or 2-butenyl group. Optional substituents which may be present on such groups include one or more C_{1-6}alkoxy, e.g. methoxy, ethoxy, propoxy, C_{1-6}alkylthio, e.g. methylthio, ethylthio, propylthio, amino, substituted amino [such as $-NHR^{15}$ where R^{15} is as defined above], carboxyl or $-CO_2R^{13}$ [where R^{13} is as defined above] groups.

Cycloalkyl groups represented by the group R^2 in compounds according to the invention include C_{3-8}cycloalkyl groups such as cyclopentyl or cyclohexyl groups.

When the group R^2 in compounds of formula (1) is a substituted amino group, this may be for example a group $-NHR^{15}$ where R^{15} is as defined above.

When R^2 is a cycloalkylalkyl group it may be for example a C_{3-8}cycloalkylC_{1-6}alkyl group such as a cyclopentylC_{1-6}alkyl or cyclohexyl-C_{1-6}alkyl group, for example a cyclopentylmethyl, cyclopentylethyl,

The group R^7 and/or R^8 in compounds of formula (1) may each be a hydrogen atom or an optionally substituted straight or branched C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or i-butyl, C_{6-12}aryl, e.g. phenyl, or C_{6-12}arylC_{1-6}alkyl, e.g. benzyl, phenylethyl or phenylpropyl group. Optional substituents present on alkyl groups of this type include one or more C_{1-6}alkoxy, e.g. methoxy or ethoxy, or C_{1-6}alkylthio, e.g. methylthio or ethylthio groups or an optionally substituted C_{6-12}aryloxy e.g. phenyloxy, C_{6-12}arylthio e.g. phenylthio, C_{6-12}arylC_{1-6}alkoxy e.g. benzyloxy or C_{6-12}arylC_{1-6}alkylthio e.g. benzylthio. Optional substituents present on the group R^7 or R^8 when it is an aryl or aralkyl group or an alkyl group substituted by an aryloxy or arylthio group include R^{16} groups as defined below.

When the group R^1 in compounds of formula (1) represents an optionally substituted alkyl or alkenyl group, it may be, for example, a straight or branched C_{1-6} alkyl or C_{2-6}alkenyl group, such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, ethenyl, 1-propenyl, 1-butenyl or 2-butenyl group optionally substituted by one or more C_{1-6}alkoxy, e.g. methoxy, ethoxy, propoxy, C_{1-6}alkylthio, e.g. methylthio, ethylthio, propylthio, C_{6-12}arylC_{1-6}alkoxy, e.g. phenylC_{1-6}alkoxy such as benzyloxy, aralkylthio, e.g. phenyl-C_{1-6}alkylthio such as benzylthio, amino ($-NH_2$), substituted amino, [such as $-NHR^{15}$, where R^{15} is a C_{1-6} alkyl e.g. methyl or ethyl, C_{6-12}aryl-C_{1-6}alkyl, e.g. phenylC_{1-6}alkyl, such as benzyl, C_{6-12}aryl, e.g. phenyl, C_{3-8}cycloalkyl, e.g. cyclohexyl, or C_{3-8}cycloalkylC_{1-6}alkyl, e.g. cyclohexylmethyl group], carboxyl ($-CO_2H$) or $-CO_2R^{13}$ [where R^{13} is as defined above] groups.

Aryl groups represented by R^1 and/or R^2 in compounds of formula (1) include optionally substituted mono- or bicyclic C_{6-12} aryl groups such as phenyl or 1- or 2-naphthyl groups.

Aralkyl groups represented by R^1 include optionally substituted mono- or bicyclic C_{6-12}arylC_{1-6}alkyl groups such as phenylC_{1-6}alkyl, or 1- or 2-naphthylC_{1-6}alkyl, for example benzyl, phenylethyl, phenylpropyl, phenylbutyl, phenylpentyl, 1- or 2- naphthylmethyl, naphthylethyl,

n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, α-naphthylmethyl or β-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, α-naphthyl or β-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, α-naphthyloxymethyl or β-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the groups R^{13} include for example one or more halogen atoms such as fluorine, chlorine, bromine or iodine atoms, or C_{1-4}alkyl, e.g. methyl or ethyl, or C_{1-4}alkoxy, e.g. methoxy or ethoxy, groups.

In general, when the group R represents an esterified carboxyl group, it may be a metabolically labile ester of a carboxylic acid.

When the group R^6 in compounds of formula (1) represents an acyl group, it may be for example a group of formula $R^{14}C=X^3$ where X^3 is an oxygen or sulphur atom and R^{14} represents a hydrogen atom or a group selected from amino ($-NH_2$), substituted amino (for example a group $-NR^{17}R^{18}$ as described below in relation to the group X), or an optionally substituted C_{1-6}alkyl, C_{1-6}alkoxy,C_{1-6}alkythio, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{6-12}aryl, C_{6-12}aralkyl, C_{3-6}cycloalkyl, C_{3-6}heteroaryl or C_{3-6}heteroaralkyl group. Particular groups of these types include optionally substituted methyl, ethyl, n-propyl, i-propyl, methoxy, ethoxy, methylthio, ethylthio, ethenyl, 1-propenyl, ethynyl, 1-propynyl, phenyl, 1-naphthyl, 2-naphthyl, benzyl, phenethyl, 1-naphthylmethyl, 2-naphthylmethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, furanyl, pyrrolyl, thienyl, furanylmethyl, pyrrolylmethyl or thienylmethyl groups. Optional substituents which may be present on such R^{14} groups include one or more substituents selected from those described below in relation to the group R^1 or R^2 when such groups represent substitued alkyl, aryl or heteroaryl groups.

R^5 represents a group $-C(R^9)(R^{10})Het-R^{11}$, wherein R^9 and R^{10} which may be the same or different is each an optionally substituted alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms or $-N(R^{12})-$ groups (where R^{12} is a hydrogen atom or an optionally substituted alkyl group), or an optionally substituted cycloalkyl, cycloalkenyl, aryl or heteroaryl group, or R^9 and R^{10} together with the carbon atom to which they are attached are linked together to form an optionally substituted cycloalkyl or cycloalkenyl group, Het is -O-, $-S(O)_p-$ [where p is zero, or an integer 1 or 2] or $-N(R^{12})-$, and R^{11} is a hydrogen atom or an aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic, or heteroaromatic group;

X is an amino ($-NH_2$), substituted amino, hydroxyl or substituted hydroxyl group, or is linked to the atom or group Het in R^5 to form a chain -X-Alk-R^5- where X is $-N(R^{12})-$, Alk is an optionally substituted alkylene chain and R^5 is $-Het-C(R^9)(R^{10})-$;

and the salts, solvates, hydrates and prodrugs thereof.

It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms, for example those marked with an asterisk in formula (1). The presence of one or more of these aysmmetric centres in a compound of formula (1) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereoisomers, and mixtures, including racemic mixtures, thereof.

In the formulae herein, the ~line is used at a potential asymmetric centre to represent the possibility of R- and S- configurations, the ⟸ line and the ------- line to represent an unique configuration at an asymmetric centre.

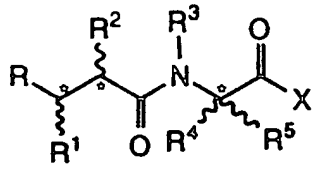
In the compounds according to the invention, when the group R represents an esterified carboxyl group, it may be for example a group of formula $-CO_2R^{13}$ where R^{13} is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl,

pharmaceutically acceptable doses. What is therefore needed is a potent orally active compound with a good duration of action.

SUMMARY OF THE INVENTION

We have now found a new class of peptidyl derivatives, members of which are metalloproteinase inhibitors. The compounds according to the invention have surprisingly good oral bioavailability, and after oral administration have an advantageously longer duration of action than related known compounds, such as those described in International Patent Specification No. WO92/09564.

Thus according to one aspect of the invention we provide a compound of formula (1)



(1)

wherein R represents a -CONHOR^6 [where R^6 is a hydrogen atom or an acyl group], carboxyl (-CO_2H), esterified carboxyl, -SR^6 or -P(O)(X^{1}R^7)-X^{2}R^8 group, where X^1 and X^2, which may be the same or different, is each an oxygen or sulphur atom and R^7 and R^8, which may be the same or different each represents a hydrogen atom or an optionally substituted alkyl, aryl, or aralkyl group;

R^1 represents a hydrogen atom or an optionally substituted alkyl, alkenyl, aryl, aralkyl, heteroaralkyl or heteroarylthioalkyl group;

R^2 represents an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, amino (-NH_2), substituted amino, carboxyl (-CO_2H), or esterified carboxyl group;

R^3 represents a hydrogen atom or an alkyl group;

R^4 represents a hydrogen atom or an alkyl group;

PEPTIDYL DERIVATIVES AND THEIR USE AS METALLOPROTEINASE INHIBITORS

FIELD OF THE INVENTION

This invention relates to a novel class of peptidyl derivatives, to processes for their preparation and to their use in medicine.

BACKGROUND TO THE INVENTION

In normal tissues, cellular connective tissue synthesis is offset by extracellular matrix degradation, the two opposing effects existing in dynamic equilibrium. Degradation of the matrix is brought about by the action of proteinases released from resident connective tissue cells and invading inflammatory cells, and is due, in part, to the activity of at least three groups of metalloproteinases. These are the collagenases, the gelatinases (or type-IV collagenases) and the stromelysins. Normally these catabolic enzymes are tightly regulated at the level of their synthesis and secretion and also at the level of their extracellular activity, the latter through the action of specific inhibitors, such as α_2-macroglobulins and TIMP (tissue inhibitor of metalloproteinase), which form inactive complexes with metalloproteinases.

The accelerated, uncontrolled breakdown of connective tissues by metalloproteinase catalysed resorption of the extracellular matrix is a feature of many pathological conditions, such as rheumatoid arthritis, corneal, epidermal or gastric ulceration; tumour metastasis or invasion; periodontal disease and bone disease. It can be expected that the pathogenesis of such diseases is likely to be modified in a beneficial manner by the administration of metalloproteinase inhibitors and numerous compounds have been suggested for this purpose [for a general review see Wahl, R.C. et al Ann. Rep. Med. Chem. 25, 175-184, Academic Press Inc., San Diego (1990)].

Although numerous metalloproteinase inhibitors have been described, many have not been suitable for further development as medicines since they have lacked any us ful activity wh n administered orally at

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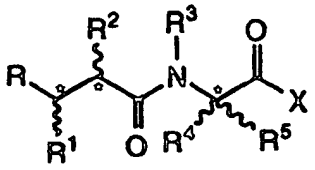
(57) Abstract



(1)

Compounds of formula (1), wherein R represents a -CONHOR^6 [where R^6 is a hydrogen atom or an acyl group], carboxyl (-CO_2H), esterified carboxyl, -SR^6 or -P(O)(X^{1}R^7)-X^{2}R^8 group, where X^1 and X^2, which may be the same or different, is each an oxygen or sulphur atom and R^7 and R^8, which may be the same or different each represents a hydrogen atom or an optionally substituted alkyl, aryl, or aralkyl group; R^1 represents a hydrogen atom or an optionally substituted alkyl, alkenyl, aryl, aralkyl, heteroaralkyl or heteroarylthioalkyl group; R^2 represents an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, amino (-NH_2), substituted amino, carboxyl (-CO_2H), or esterified carboxyl group; R^3 represents a hydrogen atom or an alkyl group; R^4 represents a hydrogen atom or an alkyl group; R^5 represents a group -C(R^9)(R^{10})Het-R^{11}, wherein R^9 and R^{10} which may be the same or different is each an optionally substituted alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R^{12})- groups (where R^{12} is a hydrogen atom or an optionally substituted alkyl group), or an optionally substituted cycloalkyl, cycloalkenyl, aryl or heteroaryl group, or R^9 and R^{10} together with the carbon atom to which they are attached are linked together to form an optionally substituted cycloalkyl or cycloalkenyl group, Het is -O-, -S(O)$_p$- [where p is zero, or an integer 1 or 2] or -N(R^{12})-, and R^{11} is a hydrogen atom or an aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic, or heteroaromatic group; X is an amino (-NH_2), substituted amino, hydroxyl or substituted hydroxyl group, or is linked to the atom or group Het in R^5 to form a chain -X-Alk-R^5- where X is -N(R^{12})-, Alk is an optionally substituted alkylene chain and R^5 is -Het-C(R^9)(R^{10})-; and the salts, solvates, hydrates and prodrugs thereof. The compounds are orally active metalloproteinase inhibitors, with a good duration of action and may be of use in the prophylaxis or treatment of diseases or disorders in which stromelysin, collagenase and gelatinase have a role, for example in the treatment of cancer to control the development of tumor metastases.